

### **REMARKS**

Entry of this amendment and reconsideration of the subject application in view thereof are respectfully requested.

#### ***I. Claim Status***

Claims 1-15 are pending in the application. These claims have been rejected. Claim 15 has been amended to overcome the objection. No new matter is added.

#### ***II. Rejections Under 35 U.S.C. § 103***

Claims 1-15 stood rejected under 35 U.S.C. § 103(a) as being unpatentable over WO -A- 95 10514 (“WO 95”), Iwasaki et al., 1999, Chemical And Pharmaceutical Bulletin, JP (11-1999), Vol.42, pages 2285-2290 (“Iwasaki”) Sejas et al., 1998, Tetrahedron, 44:6197-6200 (“Sejas”) WO-A-9631478 (“WO 96”), EP 0,208,855 (“EP ‘855”), EP 0,152,897 (“EP ‘897”), US 4,659,716 (“‘716 patent”), or HU 194,864 (“HU ‘864”) independently and also all in view of Peon et al., 2002, J. Am. Chem. Soc. 124:6428-6438 (“Peon”). Applicant respectfully traverses this rejection.

Claim 1 is an independent claim, which is a process for the production of Desloratadine by “reacting starting compound loratadine with neat alcohol in presence of inorganic base, and isolating the title compound in crystalline form by conventional methods on addition of excess water.”

First, Applicant maintains its arguments made in the paper dated September 25, 2007 filed in response to the Office Action of Jun 27, 2007 and against the cited art. Further, Applicant respectfully believes that this rejection has been overcome in view of the discussion herein.

Applicant respectfully submits again that the rejection on obviousness grounds cannot be sustained by mere conclusory statements (e.g., the statement that “[u]sing neat alcohol instead of aqueous make the fuel cell more efficient and faster according to Peon Jorge et al.,” made at page 3 of the Office Action). Particularly, with regard to Peon, the Examiner appears to have misconstrued this reference. Peon does not teach or suggest that using neat alcohol instead of aqueous makes the fuel cell more efficient and faster. It reports that protonation fraction

decreases from methanol to 2-propanol due to decreased branching ratio for protonation in the less acidic alcohols. The abstract concludes that “[s]inglet carbenes are powerful, photogenerated bases that open new possibilities for fundamental studies of proton transfer in solution.” Neither the title nor the description in this reference suggests anything about a process of making desloratadine from loratadine in the presence of a neat alcohol. Peon is about protonation of diphenylcarbene in singlet state and rate of protonation in alcohols.

To the extent the Examiner wishes to continue to rely on Peon for establishing obviousness based on the argument that “[u]sing neat alcohol instead of aqueous make the fuel cell more efficient and faster,” this argument too should fail because Peon suggests just the opposite. See, Peon at 6436 where it teaches that

The fastest known photoacids transfer a proton to a water molecule in slightly less than 10 ps. Excited-state proton transfer to H<sub>2</sub>O occurs in  $8 \pm 1$  ps at 25 °C for 5-cyano-1-naphthol . . . and in 7.1 ps for 7-hydroxy-4-methylflavylium . . . Proton transfer from excited 8-hydroxypyrene-1,3,6-trisulfonate to acetate ion, which is present at high concentration in aqueous solution, occurs in 3 ps . . . Ph<sub>2</sub>C, which accepts a proton in 9 ps in neat methanol . . . Interestingly, proton transfer to methanol by 5-cyano-1-naphthol is nearly 2 orders of magnitude slower than in water, requiring 390 in CH<sub>3</sub>OH.

For ethanol and propanol, the “ps” is even higher than that for methanol. See Peon, Table 2 at 6435. It is clear that the proton transfer is faster (in 3 ps or “2 orders of magnitude” higher) in “aqueous” environment, than in “neat alcohol” (and hence “aqueous make[s] the fuel cell more efficient and faster”). Thus, Peon clearly teaches contrary to the Examiner’s characterization of the reference. In view of this teaching, the motivation to use aqueous alcohol rather than a neat alcohol in a process to make the process more efficient is clearly provided. For these reasons, any rejection based on Peon cannot be maintained.

With regard to the ‘716 patent, it suggest the use of KOH and EtOH/Water (1:1) for 66 hrs or NaOH and 70% EtOH for 24 hrs with yield ranging from 90 to 95%. It does not teach or suggest the claimed process for the production of desloratadine by reacting loratadine with neat alcohol in the presence of inorganic base and isolating desloratadine in crystalline form by the addition water to the reaction mixture. With regard to the “neat alcohol” limitation, the

Examiner appears to admit that '716 patent does not teach or suggest that limitation when the reference is considered independently. However, the Examiner appears to contend that the '716 patent in combination with the Peon reference (see the Office Action at 5, where it is stated that "[t]he Jorge reference just explains the mechanism with the neat alcohol") suggests the claimed process. But Peon, for reasons discussed fully above, does not and cannot remedy the deficiencies in the '716 patent. Thus, the combination of the '716 patent with Peon would not have suggested making the specific modifications necessary to achieve the claimed process. Further, the claimed process can be completed in a significantly shorter time period (see, for example, Example 1) than that suggested by the '716 patent. Therefore, the '716 patent and Peon cannot render claim 1 obvious.

With regard to the US 5595997<sup>1</sup> (the '997 patent), it teaches saponification of loratadine at column 11, lines 6-14 as follows:

Loratadine (4.0 g) was added to a solution of sodium hydroxide (5.9 g) in 280 mL of absolute ethanol and the mixture was stirred at reflux for four days. The mixture was cooled and concentrated to remove ethanol. The residue was diluted with water and aqueous layer was extracted with methylene chloride five times. The combined organic layer was washed with water, brine and dried over sodium sulfate. The solvent was evaporated to give 2.82 g (87%) of pure loratadine derivative (or metabolite) as a pale-tan solid.

It does not teach or suggest the claimed process for the production of desloratadine by reacting loratadine with neat alcohol in presence of inorganic base and isolating desloratadine in crystalline form by the addition water to the reaction mixture. If anything, it teaches away not toward, the claimed process. It teaches a process requiring, among other things, removal of ethanol and extractions with methylene chloride. Further, it teaches a process requiring at least four days. Furthermore, the product obtained is "pale-tan solid." In contrast, Applicant is

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<sup>1</sup> The Examiner's reference to "US 5595957" at page 5 of the Office Action has been noted. This patent concerns turf and soil drought stress treatment. Therefore, it was understood by the Applicant that the reference is actually to US 5595997, which patent was "disclosed in the specification . . ." at page 4, lines 15-17 and also at page 6, lines 23-25.

claiming an improved process without requiring removal of ethanol or extractions with methylene chloride and the claimed process can be completed in a significantly shorter time period (see, for example, Example 1) than that suggested by the '997 patent, and the product obtained is not colored. Peon, discussed above, does not and cannot remedy the deficiencies in the '997 patent. Thus, the '997 patent alone or the '997 patent in combination with Peon would not have suggested making the specific modifications necessary to achieve the claimed process. Therefore, the '997 patent and Peon cannot render claim 1 obvious.

With regard to crystallization, Applicant recites a specific isolation step (requiring only "addition of excess water") as part of the "improved process for the production of Desloratadine," which is not taught or suggested by the cited prior art references.

At page 5 of the Office Action, the Examiner avers that "Applicants modifications are so important that the examiner is having hard time articulating what is well known in the art." However, this is not sufficient. To support a rejection under 35 U.S.C. 103, there must be a clear articulation of the reasons why the claimed invention would have been obvious. The Examiner has not provided a sufficient reason or explicit analysis of why the cited prior art references should be modified so as to arrive at the claimed invention. The Examiner cannot impermissibly use the instant claims as a guide or roadmap in formulating the rejection. Therefore, the Examiner's obviousness rejection is believed to stand in error.

In view of the foregoing, Applicant respectfully submits that the Examiner has not established a *prima facie* case of obviousness of the independent claim 1 under 35 U.S.C. § 103(a). Even if *prima facie* obviousness has been established, which it has not, it is urged that the cited art nonetheless fails to render the present invention obvious under a proper § 103 analysis, as the proper suggestions and motivations are lacking in the cited reference.

Applicant also submits that the Examiner has not established a *prima facie* case of obviousness of dependent claims 2-15 under 35 U.S.C. § 103(a). The rejected dependent claims 2-15, and the newly added claims 16-20, by virtue of their dependency (either directly or indirectly) from the independent claim 1 are similarly considered by Applicant to patentably define themselves over the cited reference. Reconsideration is respectfully requested.

Serial No.: 10/529,008

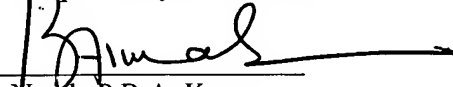
**III. Conclusion**

Applicant believes this response to be a full and complete response to the Office Action. Accordingly, favorable reconsideration in view of this response and allowance of all of the pending claims are earnestly solicited.

If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

Date: April 21, 2008

Respectfully submitted,



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